

09/25/2005 10669738.trn

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PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
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NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT
MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
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*FEDRIP - Federal Research in Progress Database

* The files listed above are temporarily unavailable.

FILE 'HOME' ENTERED AT 14:54:10 ON 25 SEP 2005

=>

Uploading

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE

Do you want to switch to the Registry File?

Choice (Y/n):

10669738.trn

Page 1

14:57

09/25/2005 10669738.trn

Switching to the Registry File...

Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 14:54:31 ON 25 SEP 2005
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STRUCTURE FILE UPDATES: 23 SEP 2005 HIGHEST RN 863870-12-6
DICTIONARY FILE UPDATES: 23 SEP 2005 HIGHEST RN 863870-12-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

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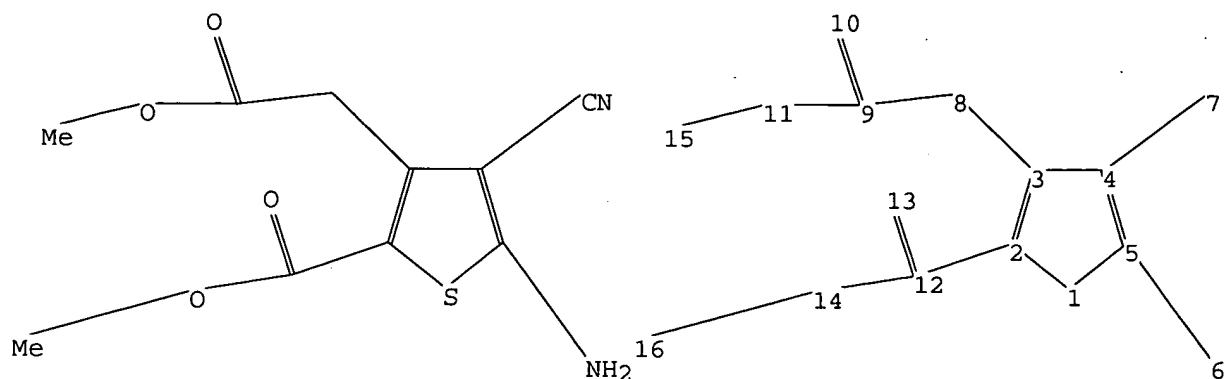
*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=>

Uploading C:\Program Files\Stnexp\Queries\10669738.str



chain nodes :

6 7 8 9 10 11 12 13 14 15 16

ring nodes :

1 2 3 4 5

chain bonds :

2-12 3-8 4-7 5-6 8-9 9-10 9-11 11-15 12-13 12-14 14-16

ring bonds :

1-2 1-5 2-3 3-4 4-5

exact/norm bonds :

5-6 9-10 9-11 12-13 12-14

exact bonds :

1-2 1-5 2-3 2-12 3-4 3-8 4-5 4-7 8-9 11-15 14-16

isolated ring systems :

containing 1 :

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS

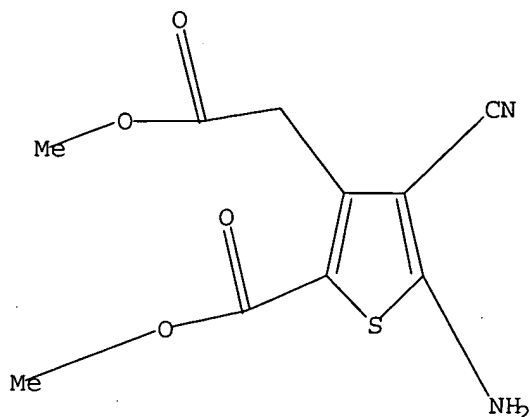
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L1 STRUCTURE UPLOADED

=> d 11

L1 HAS NO ANSWERS

L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 14:54:46 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED 0 ITERATIONS
SEARCH TIME: 00.00.01

0 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 0 TO 0
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 sss full

FULL SEARCH INITIATED 14:54:52 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 38 TO ITERATE

100.0% PROCESSED 38 ITERATIONS
SEARCH TIME: 00.00.01

1 ANSWERS

L3 1 SEA SSS FUL L1

=> FIL HCAPLUS

~~COST IN U.S. DOLLARS~~

SINCE FILE	TOTAL
ENTRY	SESSION
161.33	161.54

FULL ESTIMATED COST

FILE 'HCAPLUS' ENTERED AT 14:54:57 ON 25 SEP 2005
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FILE COVERS 1907 - 25 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 23 Sep 2005 (20050923/ED)

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l3

L4

2 L3

=> d l4 ibib abs hitstr tot

L4 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:253137 HCAPLUS

DOCUMENT NUMBER: 140:287258

TITLE: Process for the industrial-scale synthesis of the
methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-
thiophenecarboxylic acid and its application to the
synthesis of bivalent salts of ranelic acid and their
hydrates

INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois,
Pascal

PATENT ASSIGNEE(S):

SOURCE: U.S. Pat. Appl. Publ., 4 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

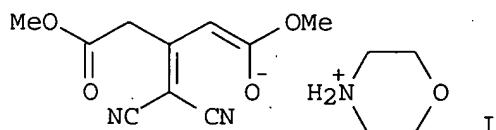
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059135	A1	20040325	US 2003-669738	20030924
FR 2844796	A1	20040326	FR 2002-11764	20020924
EP 1403264	A1	20040331	EP 2003-292317	20030922
EP 1403264	B1	20041229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029035	A1	20040408	WO 2003-FR2776	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
BR 2003004194	A	20040908	BR 2003-4194	20030922
JP 2004269495	A2	20040930	JP 2003-330438	20030922

AT 286041	E	20050115	AT 2003-292317	20030922
ES 2235144	T3	20050701	ES 2003-3292317	20030922
CA 2442875	AA	20040324	CA 2003-2442875	20030923
NZ 528400	A	20040625	NZ 2003-528400	20030923
ZA 2003007410	A	20040707	ZA 2003-7410	20030923
CN 1500783	A	20040602	CN 2003-134807	20030924
SG 110070	A1	20050428	SG 2003-5554	20030924
PRIORITY APPLN. INFO.:			FR 2002-11764	A 20020924
OTHER SOURCE(S):		CASREACT 140:287258		
GI				



AB The Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid is prepared on an industrial scale via the condensation reaction of di-Me 3-oxoglutarate with malonitrile in methanol in the presence of 0.95 mol of morpholine per mol of di-Me 3-oxoglutarate to give the morpholinium salt (I) which is subjected to a cyclocondensation reaction with 0.95 mol of sulfur per mol of di-Me 3-oxoglutarate, the reaction is heated at reflux, water added, and the title compound precipitated and collected by filtration. Application of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid to the synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

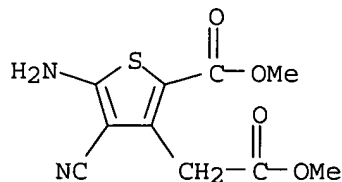
IT 674773-12-7P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(process for the industrial-scale synthesis of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates)

RN 674773-12-7 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(methoxycarbonyl)- methyl ester
(9CI) (CA INDEX NAME)



L4 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:249307 HCAPLUS

DOCUMENT NUMBER: 140:272696

TITLE: New process for industrial synthesis of strontium ranelate and its hydrates

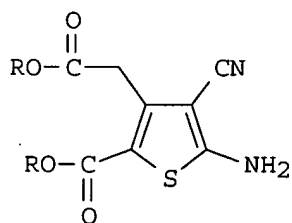
INVENTOR(S): Vaysse, Ludot Lucile; Lecouve, Jean Pierre; Langlois, Pascal

PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.
 SOURCE: Fr. Demande, 22 pp.
 CODEN: FRXXBL
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

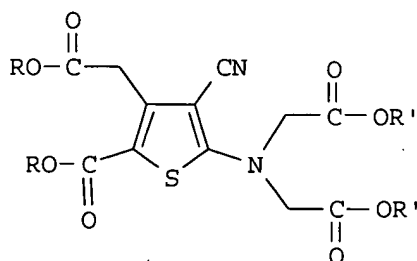
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2844795	A1	20040326	FR 2002-11763	20020924
FR 2844795	B1	20041022		
EP 1403266	A1	20040331	EP 2003-292319	20030922
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WO 2004029036	A1	20040408	WO 2003-FR2777	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004149516	A2	20040527	JP 2003-330440	20030922
CA 2442878	AA	20040324	CA 2003-2442878	20030923
ZA 2003007409	A	20040707	ZA 2003-7409	20030923
NZ 528402	A	20040730	NZ 2003-528402	20030923
BR 2003004213	A	20040831	BR 2003-4213	20030923
US 2004063972	A1	20040401	US 2003-669301	20030924
CN 1496986	A	20040519	CN 2003-134813	20030924
SG 110071	A1	20050428	SG 2003-5555	20030924
PRIORITY APPLN. INFO.:			FR 2002-11763	A 20020924

OTHER SOURCE(S): MARPAT 140:272696

GI



I



II

AB An industrial process for the synthesis of strontium ranelate and its hydrates consists of: reaction of $\text{RO}_2\text{CCH}_2\text{COCH}_2\text{CO}_2\text{R}$ (R = linear or branched C1-6 alkyl) with malononitrile (NCCH_2CN) in MeOH in presence of morpholine (>0.95 mol per mol diester) to give the morpholinium salt of $\text{ROCOCH}_2\text{C}[:\text{C}(\text{CN})_2]\text{CH}:\text{C}(\text{OR})\text{O}-$, followed by refluxing with sulfur to give thiophene derivative I (same R). Reaction of the latter (as diacid) with

BrCH₂CO₂R' (R' = e.g., Me or Et) in the presence of a catalytic quantity of C₈-10 quaternary ammonium salt and K₂CO₃ in an organic solvent at reflux affords tetracarboxylate II, which reacts with Sr(OH)₂ at reflux in water for ≥ 5 h to give strontium ranelate and its hydrates. Thus, the octahydrate of strontium ranelate was prepared by this method (96% yield and 98% purity in final step).

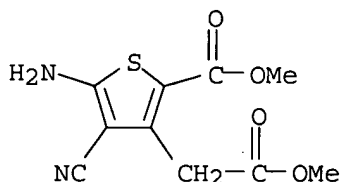
IT 674773-12-7P

RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)

(for industrial preparation of strontium ranelate and its hydrates)

RN 674773-12-7 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL REGISTRY

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
17.23	178.77

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-1.46	-1.46

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STRUCTURE FILE UPDATES: 23 SEP 2005 HIGHEST RN 863870-12-6

DICTIONARY FILE UPDATES: 23 SEP 2005 HIGHEST RN 863870-12-6

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TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

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*

*

* The CA roles and document type information have been removed from *

* the IDE default display format and the ED field has been added, *

09/25/2005 10669738.trn

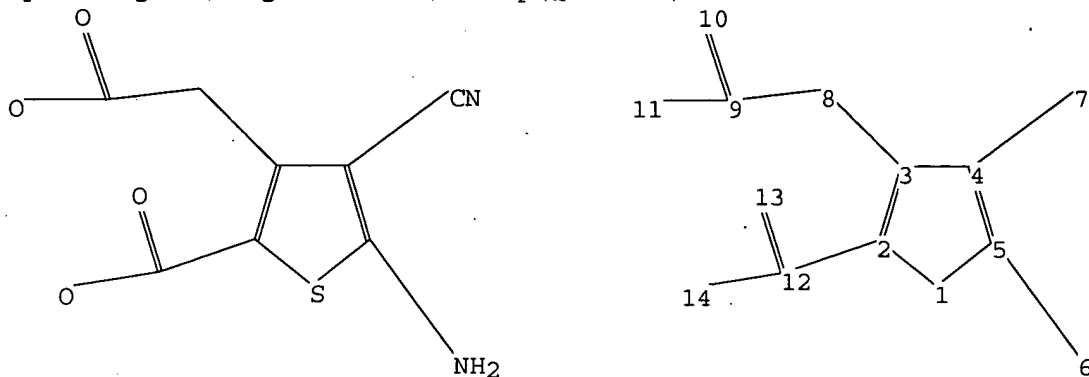
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=>

Uploading C:\Program Files\Stnexp\Queries\10669738a.str



chain nodes :

6 7 8 9 10 11 12 13 14

ring nodes :

1 2 3 4 5

chain bonds :

2-12 3-8 4-7 5-6 8-9 9-10 9-11 12-13 12-14

ring bonds :

1-2 1-5 2-3 3-4 4-5

exact/norm bonds :

5-6 9-10 9-11 12-13 12-14

exact bonds :

1-2 1-5 2-3 2-12 3-4 3-8 4-5 4-7 8-9

isolated ring systems :

containing 1 :

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS

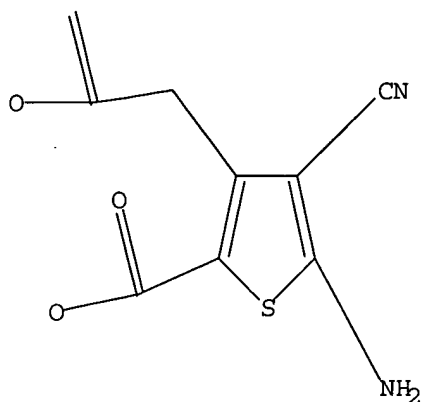
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS

L5 STRUCTURE UPLOADED

=> d 15

L5 HAS NO ANSWERS

L5 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 15

SAMPLE SEARCH INITIATED 14:56:53 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED 0 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 0 TO 0
PROJECTED ANSWERS: 0 TO 0

L6 0 SEA SSS SAM L5

=> s 15 sss full

FULL SEARCH INITIATED 14:56:59 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 63 TO ITERATE

100.0% PROCESSED 63 ITERATIONS
SEARCH TIME: 00.00.01

3 ANSWERS

L7 3 SEA SSS FUL L5

=> FIL HCAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
	161.33	340.10
FULL ESTIMATED COST		
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
	0.00	-1.46
CA SUBSCRIBER PRICE		

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FILE COVERS 1907 - 25 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 23 Sep 2005 (20050923/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 17

L8

10 L7

=> s 18 and process

2149075 PROCESS

1438162 PROCESSES

3197607 PROCESS

(PROCESS OR PROCESSES)

L9

3 L8 AND PROCESS

=> d 18 ibib abs hitstr tot

L8. ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:253137 HCAPLUS

DOCUMENT NUMBER: 140:287258

TITLE: Process for the industrial-scale synthesis of the methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates

INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal

PATENT ASSIGNEE(S): FR.

SOURCE: U.S. Pat. Appl. Publ., 4 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

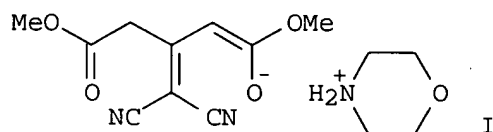
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FR 2844796	A1	20040326	FR 2002-11764	20020924
EP 1403264	A1	20040331	EP 2003-292317	20030922
EP 1403264	B1	20041229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029035	A1	20040408	WO 2003-FR2776	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
 PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
 TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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JP 2004269495	A2	20040930	JP 2003-330438	20030922
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ES 2235144	T3	20050701	ES 2003-3292317	20030922
CA 2442875	AA	20040324	CA 2003-2442875	20030923
NZ 528400	A	20040625	NZ 2003-528400	20030923
ZA 2003007410	A	20040707	ZA 2003-7410	20030923
CN 1500783	A	20040602	CN 2003-134807	20030924
SG 110070	A1	20050428	SG 2003-5554	20030924
PRIORITY APPLN. INFO.:			FR 2002-11764	A 20020924

OTHER SOURCE(S): CASREACT 140:287258

GI



AB The Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid is prepared on an industrial scale via the condensation reaction of di-Me 3-oxoglutarate with malonitrile in methanol in the presence of 0.95 mol of morpholine per mol of di-Me 3-oxoglutarate to give the morpholinium salt (I) which is subjected to a cyclocondensation reaction with 0.95 mol of sulfur per mol of di-Me 3-oxoglutarate, the reaction is heated at reflux, water added, and the title compound precipitated and collected by filtration. Application of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid to the synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

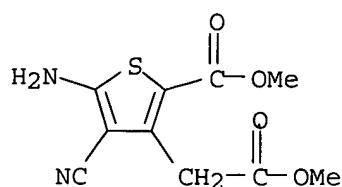
IT **674773-12-7P**

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(process for the industrial-scale synthesis of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates)

RN 674773-12-7 HCAPLUS

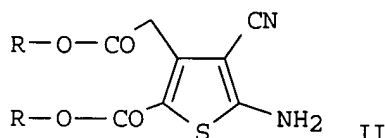
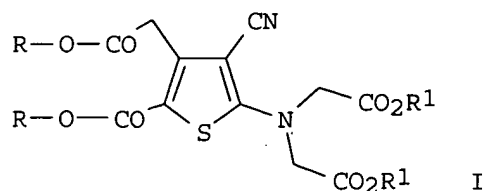
CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)



L8 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS OR STN
 ACCESSION NUMBER: 2004:252227 HCAPLUS
 DOCUMENT NUMBER: 140:270729
 TITLE: Process for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and their application to the synthesis of bivalent salts of ranelic acid and their hydrates
 INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal
 PATENT ASSIGNEE(S): Fr.
 SOURCE: U.S. Pat. Appl. Publ., 4 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059134	A1	20040325	US 2003-669302	20030924
FR 2844797	A1	20040326	FR 2002-11765	20020924
FR 2844797	B1	20041022		
EP 1403265	A1	20040331	EP 2003-292318	20030922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029034	A1	20040408	WO 2003-FR2775	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004269496	A2	20040930	JP 2003-330439	20030922
CA 2442881	AA	20040324	CA 2003-2442881	20030923
NZ 528401	A	20040528	NZ 2003-528401	20030923
ZA 2003007411	A	20040707	ZA 2003-7411	20030923
BR 2003004203	A	20040824	BR 2003-4203	20030923
CN 1500784	A	20040602	CN 2003-134812	20030924
SG 110069	A1	20050428	SG 2003-5553	20030924
PRIORITY APPLN. INFO.: FR 2002-11765			A	20020924

OTHER SOURCE(S): CASREACT 140:270729; MARPAT 140:270729
 GI



AB Tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid [I; R, R1 = (un)branched C1-6 alkyl] are prepared in high yield and selectivity by the alkylation of the corresponding 5-amino compound (II) with an alkyl bromoacetate ester BrCH2CO2R1 in the presence of a catalytic amount of a quaternary ammonium compound, potassium carbonate acid scavenger at reflux in an organic solvent, the reaction mixture is then concentrated by distillation, an a nonsolvent added to cause precipitation of the product with cooling. The synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

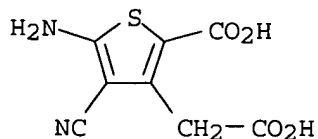
IT 674773-14-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(process for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and their application to the synthesis of bivalent salts of ranelic acid and their hydrates)

RN 674773-14-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)



L8 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:249307 HCAPLUS

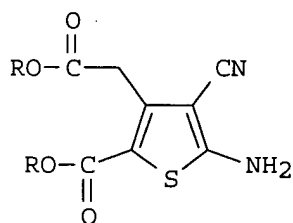
DOCUMENT NUMBER: 140:272696

TITLE: New process for industrial synthesis of strontium ranelate and its hydrates

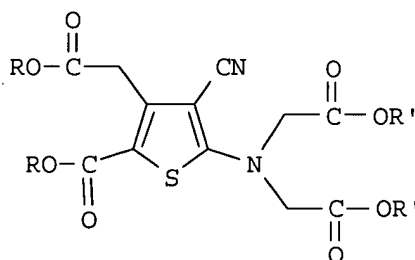
INVENTOR(S): Waisse, Ludot, Lucile; Lecouve, Jean Pierre; Langlois,

Pascal
 PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.
 SOURCE: Fr. Demande, 22 pp.
 CODEN: FRXXBL
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2844795	A1	20040326	FR 2002-11763	20020924
FR 2844795	B1	200411022		
EP 1403266	A1	20040331	EP 2003-292319	20030922
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029036	A1	20040408	WO 2003-FR2777	20030922
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004149516	A2	20040527	JP 2003-330440	20030922
CA 2442878	AA	20040324	CA 2003-2442878	20030923
ZA 2003007409	A	20040707	ZA 2003-7409	20030923
NZ 528402	A	20040730	NZ 2003-528402	20030923
BR 2003004213	A	20040831	BR 2003-4213	20030923
US 2004063972	A1	20040401	US 2003-669301	20030924
CN 1496986	A	20040519	CN 2003-134813	20030924
SG 110071	A1	20050428	SG 2003-5555	20030924
PRIORITY APPLN. INFO.:			FR 2002-11763	A 20020924
OTHER SOURCE(S):	MARPAT 140:272696			
GI				



I



II

AB An industrial process for the synthesis of strontium ranelate and its hydrates consists of: reaction of RO₂CCH₂COCH₂CO₂R (R = linear or branched C1-6 alkyl) with malononitrile (NCCH₂CN) in MeOH in presence of morpholine (>0.95 mol per mol diester) to give the morpholinium salt of ROCOCH₂C[:C(CN)₂]CH:C(OR)O-, followed by refluxing with sulfur to give

thiophene derivative I (same R). Reaction of the latter (as diacid) with $\text{BrCH}_2\text{CO}_2\text{R}'$ ($\text{R}' = \text{e.g., Me or Et}$) in the presence of a catalytic quantity of C8-10 quaternary ammonium salt and K_2CO_3 in an organic solvent at reflux affords tetracarboxylate II, which reacts with $\text{Sr}(\text{OH})_2$ at reflux in water for ≥ 5 h to give strontium ranelate and its hydrates. Thus, the octahydrate of strontium ranelate was prepared by this method (96% yield and 98% purity in final step).

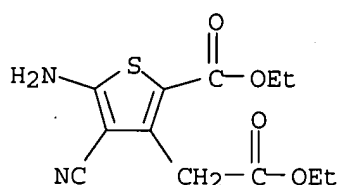
IT 58168-20-0P 674773-12-7P 674773-14-9P

RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)

(for industrial preparation of strontium ranelate and its hydrates)

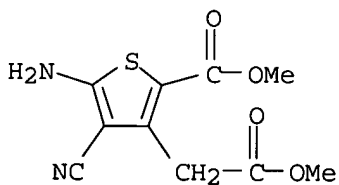
RN 58168-20-0 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester (9CI) (CA INDEX NAME)



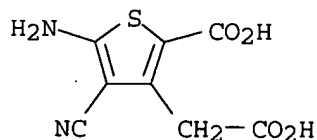
RN 674773-12-7 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)



RN 674773-14-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:116871 HCAPLUS

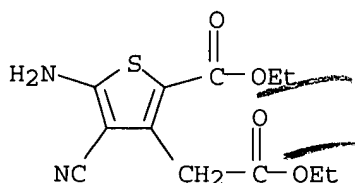
DOCUMENT NUMBER: 126:171500

TITLE: Ketene gem-dithiols; a convenient one-step procedure from aliphatic active methylenes: reactions and synthesis of polyfunctionally substituted thia- and

azaheteroaromatics
 AUTHOR(S): Zayed, Salem E.
 CORPORATE SOURCE: Dep. Chem., South Valley Univ., Kena, 83511, Egypt
 SOURCE: Phosphorus, Sulfur and Silicon and the Related
 Elements (1996), 116, 29-37
 CODEN: PSSLEC; ISSN: 1042-6507
 PUBLISHER: Gordon & Breach
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB It has been reported in the current literature that the isolation of certain ketene gem dithiols has failed due to dimerization. Generation of ketene gem-dithiols via trapping with other reactants led to formation of pyridine, pyrrole, pyridothiadiazole and pyrazolone derivs.

IT 58168-20-0P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of ketene gem-dithiols from aliphatic active methylenes)
 RN 58168-20-0 HCAPLUS
 CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester (9CI) (CA INDEX NAME)

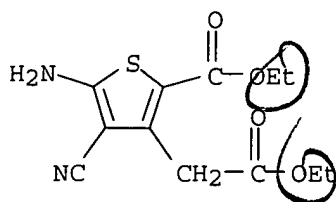


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

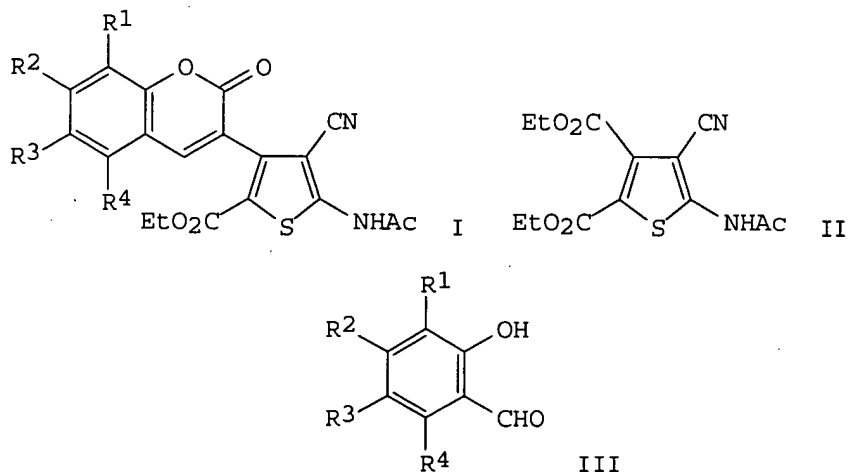
L8 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1996:512012 HCAPLUS
 DOCUMENT NUMBER: 125:170848
 TITLE: A comparison of the properties of some 2-aminothiophene-derived disperse dyes
 AUTHOR(S): Hallas, Geoffrey; Towns, Andrew D.
 CORPORATE SOURCE: Dep. Colour Chem. Dyeing, Univ. Leeds, Leeds, LS2 9JT, UK
 SOURCE: Dyes and Pigments (1996), 31(4), 273-289
 CODEN: DYPIDX; ISSN: 0143-7208
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 125:170848

AB In the course of an investigation into the properties of monoazo disperse dyes synthesized from aminothiophene diazo components, significant discrepancies were observed between the spectroscopic and fastness data of some thienyl-2-azo dyes compared to that previously reported for closely related analogs. Considerable differences in λ_{max} and ϵ_{max} values were noted; in some cases, light fastness ratings were at variance with previously disclosed figures.
 IT 58168-20-0P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (azo component; preparation and properties of 2-aminothiophene derivative)

disperse dyes)
 RN 58168-20-0 HCAPLUS
 CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester
 (9CI) (CA INDEX NAME)



L8 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1993:580624 HCAPLUS
 DOCUMENT NUMBER: 119:180624
 TITLE: Synthesis and application of 4-(coumarin-3-yl)thiophenes
 AUTHOR(S): Sabnis, Ram W.; Rangnekar, Dinesh W.
 CORPORATE SOURCE: Dep. Chem. Technol., Univ. Bombay, Bombay, 400 019, India
 SOURCE: Sulfur Letters (1993), 15(6), 263-72
 CODEN: SULED2; ISSN: 0278-6117
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 119:180624
 GI



AB A facile synthesis of (4-coumarin-3-yl)thiophenes I (R1 = H, OMe, R2 = H, OH, OMe, NEt2, R3 = H, OH, OMe, Cl, NO2, R4 = H, OMe) was achieved by the condensation of 2-acetamido-3-cyano-4-carbethoxymethylene-5-carbethoxythiophene II with selected o-hydroxy aldehydes III in the presence of piperidine. The key intermediate II was synthesized by cyclocondensation of EtO2CCH2COCH2CO2Et, sulfur, and malononitrile by a

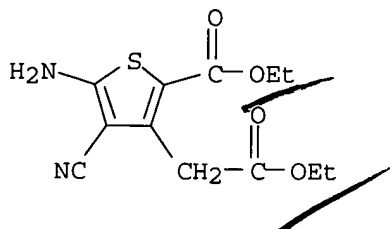
Gewald synthesis followed by acetylation. I were applied on polyester fibers as fluorescent disperse dyes and their fluorescence and dyeing properties were studied.

IT 58168-20-0

RL: RCT (Reactant); RACT (Reactant or reagent)
(N-acetylation of)

RN 58168-20-0 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester
(9CI) (CA INDEX NAME)



L8 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:429960 HCAPLUS

DOCUMENT NUMBER: 119:29960

TITLE: Novel substituted 2-acetamido thiophene-4-styryl
disperse dyes

AUTHOR(S): Rangnekar, Dinesh W.; Sabnis, Ram W.

CORPORATE SOURCE: Dep. Chem. Technol., Univ. Bombay, Bombay, 400 019,
India

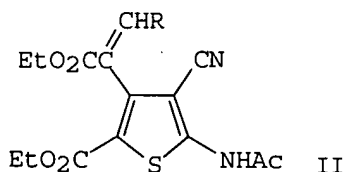
SOURCE: Journal of Chemical Technology and Biotechnology
(1993), 56(4), 401-5

CODEN: JCTBED; ISSN: 0268-2575

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB Et 2-amino-3-cyano-5-carbethoxythiophene-4-acetate was prepared and acetylated to give the acetamide derivative (I). Eight aryl and hetaryl aldehydes were condensed with I in refluxing DMF in the presence of piperidine to yield the title dyes (II; R = Ph, p-MeOC6H4, p-Me2NC6H4, p-NCC6H4, p-AcNHC6H4, 2-furyl, 2-thienyl, 2-pyrrolyl). The fluorescence in solution and dyeing properties of II on polyester were studied.

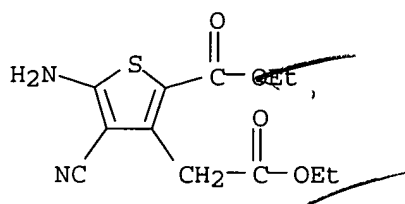
IT 58168-20-0

RL: RCT (Reactant); RACT (Reactant or reagent)
(acetylation of)

RN 58168-20-0 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester

(9CI) (CA INDEX NAME)



L8 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1992:471654 HCAPLUS

DOCUMENT NUMBER: 117:71654

TITLE: Synthesis and dyeing characteristics of ethyl 1-(2-acetamido-3-cyano-5-carbethoxythiophen-4-yl)glyoxalate(aryl)hydrazones

AUTHOR(S): Sabnis, R. W.; Rangnekar, D. W.

CORPORATE SOURCE: Dep. Chem. Technol., Univ. Bombay, Bombay, 400 019, India

SOURCE: Indian Journal of Fibre & Textile Research (1992), 17(1), 62-4

CODEN: IJFRET; ISSN: 0971-0426

DOCUMENT TYPE: Journal

LANGUAGE: English

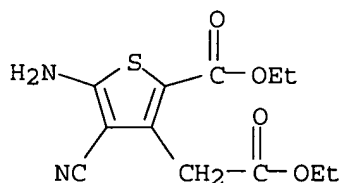
AB Five monoazo disperse dyes, Et 1-(2-acetamido-3-cyano-5-carbethoxythiophen-4-yl)glyoxalate-(aryl)hydrazones, were prepared and their dyeing performance on polyester fibers was assessed. The dyeings on polyester had orange red and bright red shades with low pickup, moderate light fastness and good sublimation fastness.

IT 58168-20-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and acetylation of)

RN 58168-20-0 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester (9CI) (CA INDEX NAME)



L8 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:200492 HCAPLUS

DOCUMENT NUMBER: 112:200492

TITLE: Synthesis of 2-azo-3-cyano-5-carbethoxy thiophene derivatives and their application on polyester fibers

AUTHOR(S): Sabnis, Ram W.; Rangnekar, Dinesh W.

CORPORATE SOURCE: Dep. Chem. Technol., Univ. Bombay, Bombay, 400 019, India

SOURCE: Journal of Chemical Technology and Biotechnology
(1990), 47(1), 39-46
CODEN: JCTBED; ISSN: 0268-2575

DOCUMENT TYPE: Journal

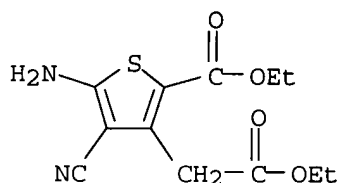
LANGUAGE: English

AB Synthesis of 2-(hetaryl or aryl)-azo thiophene derivs. was achieved by diazotization of Et 2-amino-3-cyano-5-carbethoxythiophene-4-acetate (I) using nitrosylsulfuric acid and coupling with suitable heterocyclic hydroxy and N,N-dialkyl-substituted aryl amines. I was synthesized in one pot and in excellent yield from di-Et acetonedicarboxylate, S and malonitrile, using HNEt₂ as a catalyst, following the Gewald synthesis. The spectral properties of these dyes were studied. The dyes when applied as disperse dyes on polyester fibers gave excellent results.

IT **58168-20-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and coupling of diazotized, with heterocyclic hydroxy and dialkyl-substituted aryl amines)

RN 58168-20-0 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester
(9CI) (CA INDEX NAME)



L8 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1976:59258 HCAPLUS

DOCUMENT NUMBER: 84:59258

TITLE: Reactivity of 2-aminothiophenes. Application to synthesis of thieno[2,3-b]pyrroles

AUTHOR(S): Wierzbicki, Michel; Cagniant, Denise; Cagniant, Paul

CORPORATE SOURCE: Fac. Sci., Univ. Metz, Metz, Fr.

SOURCE: Bulletin de la Societe Chimique de France (1975),
(7-8, Pt. 2), 1786-92
CODEN: BSCFAS; ISSN: 0037-8968

DOCUMENT TYPE: Journal

LANGUAGE: French

OTHER SOURCE(S): CASREACT 84:59258

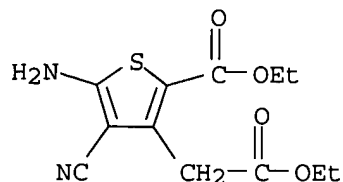
GI For diagram(s), see printed CA Issue.

AB Thienopyrroles I (R = H, Ac; R1 = OH, NH₂; R2 = CH₂CO₂Et, Me; R3 = CO₂Et, Ac) were prepared by treating the thiophenes II (R4 = H; R5 = CO₂Et, CN) with BrCH₂CO₂Et and Dieckmann reaction of II (R4 = CH₂CO₂Et). I (R1 = OH) were alkylated with BrCH₂CO₂Et or acetylated. I (R2 = NH₂) were acetylated and diazotized.

IT **58168-20-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation and reaction of, with bromoacetate)

RN 58168-20-0 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester
(9CI) (CA INDEX NAME)



=> d 19 ibib abs hitstr tot

L9 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:253137 HCAPLUS

DOCUMENT NUMBER: 140:287258

TITLE: **Process** for the industrial-scale synthesis of the methyl diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates

INVENTOR(S): Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal

PATENT ASSIGNEE(S): Fr

SOURCE: U.S. Pat. Appl. Publ., 4 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

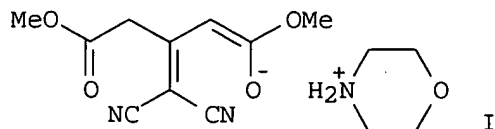
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059135	A1	20040325	US 2003-669738	20030924
FR 2844796	A1	20040326	FR 2002-11764	20020924
EP 1403264	A1	20040331	EP 2003-292317	20030922
EP 1403264	B1	20041229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2004029035	A1	20040408	WO 2003-FR2776	20030922
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BR 2003004194	A	20040908	BR 2003-4194	20030922
JP 2004269495	A2	20040930	JP 2003-330438	20030922
AT 286041	E	20050115	AT 2003-292317	20030922
ES 2235144	T3	20050701	ES 2003-3292317	20030922
CA 2442875	AA	20040324	CA 2003-2442875	20030923
NZ 528400	A	20040625	NZ 2003-528400	20030923
ZA 2003007410	A	20040707	ZA 2003-7410	20030923
CN 1500783	A	20040602	CN 2003-134807	20030924

SG 110070 A1 20050428 SG 2003-5554 20030924
 PRIORITY APPLN. INFO.: FR 2002-11764 A 20020924
 OTHER SOURCE(S): CASREACT 140:287258
 GI



AB The Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid is prepared on an industrial scale via the condensation reaction of di-Me 3-oxoglutarate with malonitrile in methanol in the presence of 0.95 mol of morpholine per mol of di-Me 3-oxoglutarate to give the morpholinium salt (I) which is subjected to a cyclocondensation reaction with 0.95 mol of sulfur per mol of di-Me 3-oxoglutarate, the reaction is heated at reflux, water added, and the title compound precipitated and collected by filtration. Application of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid to the synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

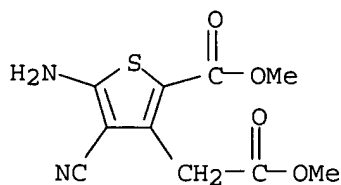
IT 674773-12-7P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(**process** for the industrial-scale synthesis of the Me diester of 5-amino-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and its application to the synthesis of bivalent salts of ranelic acid and their hydrates)

RN 674773-12-7 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(methoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)



L9 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:252227 HCAPLUS

DOCUMENT NUMBER: 140:270729

TITLE:

Process for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and their application to the synthesis of bivalent salts of ranelic acid and their hydrates

INVENTOR(S):

Vaysse-Ludot, Lucile; Lecouve, Jean-pierre; Langlois, Pascal

PATENT ASSIGNEE(S):

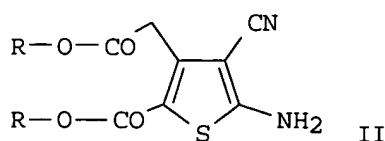
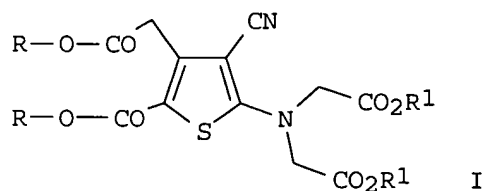
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SOURCE:

U.S. Pat. Appl. Publ., 4 pp.
 CODEN: USXXCO

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004059134	A1	20040325	US 2003-669302	20030924
FR 2844797	A1	20040326	FR 2002-11765	20020924
FR 2844797	B1	20041022		
EP 1403265	A1	20040331	EP 2003-292318	20030922
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WO 2004029034	A1	20040408	WO 2003-FR2775	20030922
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2004269496	A2	20040930	JP 2003-330439	20030922
CA 2442881	AA	20040324	CA 2003-2442881	20030923
NZ 528401	A	20040528	NZ 2003-528401	20030923
ZA 2003007411	A	20040707	ZA 2003-7411	20030923
BR 2003004203	A	20040824	BR 2003-4203	20030923
CN 1500784	A	20040602	CN 2003-134812	20030924
SG 110069	A1	20050428	SG 2003-5553	20030924
PRIORITY APPLN. INFO.:			FR 2002-11765	A 20020924
OTHER SOURCE(S):			CASREACT 140:270729; MARPAT 140:270729	
GI				



AB Tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid [I; R, R1 = (un)branched C1-6 alkyl] are prepared in high yield and selectivity by the alkylation of the corresponding 5-amino compound (II) with an alkyl bromoacetate ester BrCH₂CO₂R1 in the presence of a catalytic amount of a quaternary ammonium compound, potassium carbonate acid scavenger at reflux in an organic solvent, the reaction mixture is then concentrated by distillation, an a nonsolvent added to cause precipitation of the product with cooling. The synthesis of bivalent salts of ranelic acid, and especially strontium ranelate and its hydrates, is claimed.

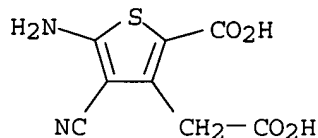
IT 674773-14-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(**process** for the industrial synthesis of tetraesters of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid and their application to the synthesis of bivalent salts of ranelic acid and their hydrates)

RN 674773-14-9 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)



L9 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:249307 HCAPLUS

DOCUMENT NUMBER: 140:272696

TITLE: New **process** for industrial synthesis of strontium ranelate and its hydrates

INVENTOR(S): Vaysse, Ludot-Lucile; Lecouve, Jean Pierre; Langlois, Pascal

PATENT ASSIGNEE(S): Les Laboratoires Servier, Fr.

SOURCE: Fr. Demande, 22 pp.

CODEN: FRXXBL

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2844795	A1	20040326	FR 2002-11763	20020924
FR 2844795	B1	20041022		
EP 1403266	A1	20040331	EP 2003-292319	20030922
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WO 2004029036	A1	20040408	WO 2003-FR2777	20030922
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				

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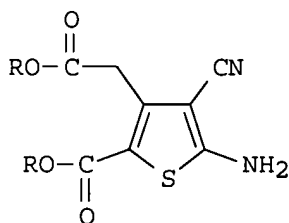
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JP 2004149516	A2	20040527	JP 2003-330440	20030922
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US 2004063972	A1	20040401	US 2003-669301	20030924
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			FR 2002-11763	A 20020924

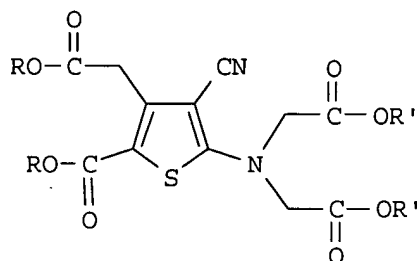
PRIORITY APPLN. INFO.:

OTHER SOURCE(S): MARPAT 140:272696

GI



I



II

AB An industrial **process** for the synthesis of strontium ranelate and its hydrates consists of: reaction of $\text{RO}_2\text{CCH}_2\text{COCH}_2\text{CO}_2\text{R}$ (R = linear or branched C1-6 alkyl) with malononitrile (NCCH_2CN) in MeOH in presence of morpholine (>0.95 mol per mol diester) to give the morpholinium salt of $\text{ROCOCH}_2\text{C}[:\text{C}(\text{CN})_2]\text{CH}:\text{C}(\text{OR})\text{O}-$, followed by refluxing with sulfur to give thiophene derivative I (same R). Reaction of the latter (as diacid) with $\text{BrCH}_2\text{CO}_2\text{R}'$ (R' = e.g., Me or Et) in the presence of a catalytic quantity of C8-10 quaternary ammonium salt and K_2CO_3 in an organic solvent at reflux affords tetracarboxylate II, which reacts with $\text{Sr}(\text{OH})_2$ at reflux in water for ≥ 5 h to give strontium ranelate and its hydrates. Thus, the octahydrate of strontium ranelate was prepared by this method (96% yield and 98% purity in final step).

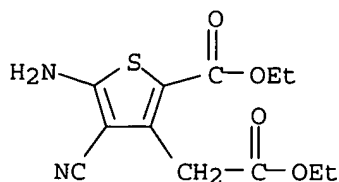
IT 58168-20-0P 674773-12-7P 674773-14-9P

RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)

(for industrial preparation of strontium ranelate and its hydrates)

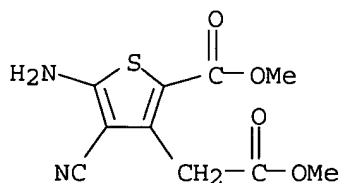
RN 58168-20-0 HCAPLUS

CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(ethoxycarbonyl)-, ethyl ester (9CI) (CA INDEX NAME)

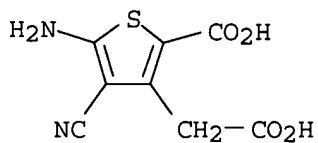


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RN 674773-12-7 HCAPLUS
CN 3-Thiopheneacetic acid, 5-amino-4-cyano-2-(methoxycarbonyl)-, methyl ester
(9CI) (CA INDEX NAME)



RN 674773-14-9 HCAPLUS
CN 3-Thiopheneacetic acid, 5-amino-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
69.12	409.22

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
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